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Efficacy of 1 and 5 mg doses of melatonin on heat tolerance while wearing NBC protective clothing

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EFFICACY OF 1 AND 5 MG DOSES OF MELATONIN ON HEAT TOLERANCE WHILE WEARING NBC PROTECTIVE CLOTHING

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Executive Summary

This report summarises the findings from 2 studies which examined whether the reported hypothermic effect of melatonin ingestion increased tolerance to the heat stress of wearing NBC protective clothing. In the first study, trials were conducted either in the morning or afternoon, 2 each in the morning (0930 h) and afternoon (1330 h) following the double-blind ingestion of either two placebo or two 1 mg capsules of melatonin. The heat stress test consisted of intermittent walking and seated rest at 40°C and 30% relative humidity while wearing NBC protective clothing. In the second study, subjects performed 4 trials which involved 2h of rest in combat clothing at either 23°C or 40°C followed by exercise at 40°C while wearing the NBC ensemble. A single 5 mg dose of melatonin was ingested following 30-min of rest. In the first study, rectal temperature (T_{re}) was not affected by melatonin ingestion but T_{re} was increased during the afternoon trials by 0.3°C compared with the morning exposures and these differences remained throughout the heat stress such that final T_{re} was also increased for the afternoon (39.2°C) versus the morning (39.0°C) trials. Since the rate of heat storage was similar, tolerance times (108, 111, 110 , and 107 min for the morning melatonin and placebo trials, and the afternoon melatonin and placebo trials, respectively) were not different among the trials. During the second study, T_{re} during rest at 23°C decreased significantly from 36.8°C to 36.7°C following the ingestion of the drug, whereas values during the placebo trial did not change. The lower T_{re} response during the melatonin trial at rest remained during the exercise in the heat while wearing the NBC protective clothing. However, since the T_{re} tolerated at exhaustion also was significantly lower for the melatonin (39.0°C) compared with the placebo (39.1°C) trial, tolerance times approximated 95 min in both conditions. During rest at 40°C, melatonin did not affect the T_{re} response which increased significantly over the rest period from 36.9°C to 37.3 °C. This increase in T_{re} during the rest period prior to donning the protective clothing decreased tolerance time approximately 30 min compared with the trials that involved prior rest at 23°C. Three conclusions evolved from these studies. First, 1 to 5 mg doses of melatonin had no impact on tolerance to the heat stress of wearing NBC protective clothing and exercising in hot environments. Second, trials conducted in the early afternoon were associated with an increased rectal temperature tolerated at exhaustion that offset the circadian influence on resting rectal temperature, and thus, maintained tolerance times similar to trials conducted in the morning. Third, elevations in core temperature that occur during rest in a hot environment significantly impaired tolerance while wearing protective clothing and exercising in the heat. The use of work and rest schedules for NBC operations can be used throughout the day but only when subjects are rested and not exposed to hot environments or conditions that elevate core temperatures prior to donning the NBC clothing.

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Introduction

In current industrial and military settings, personnel may be required to wear protective clothing to maintain work schedules in a hazardous environment. Typically the protective clothing has a reduced water vapour permeability. Thus the clothing limits the evaporation of sweat, thereby increasing the rate of heat storage for a given rate of heat production. Uncompensable heat stress develops when the evaporative heat loss required to maintain a thermal steady-state exceeds the maximum evaporative potential of the environment. It is not uncommon, therefore, for conditions which would normally be defined as compensable heat stress to become uncompensable when protective clothing is worn [1]. The heat strain associated with wearing the military's current-issue nuclear, biological and chemical (NBC) protective clothing is well documented for many countries at different ambient temperatures, vapour pressures and metabolic rates [2-8].

Tolerance time while wearing NBC protective clothing is determined from the initial core temperature, the rate of heat storage and the final core temperature tolerated at exhaustion. Unless cooling is provided, there is very little that can be done when the current NBC protective clothing is worn to alter the rate of heat storage or the core temperature tolerated at exhaustion as demonstrated following glycerol or water hyperhydration [9], water rehydration during the heat stress [10], aerobic training [11, 12] or heat acclimation [13-15]. However, factors such as aerobic fitness [14] and heat acclimation [13, 15] lower the initial core temperature 0.2 to 0.3°C and, therefore, increase tolerance time, whereas factors such as mild hypohydration [12, 14] or the post-ovulatory phase of the menstrual cycle [16, 17] raise the starting core temperature and decrease tolerance time.

The normal circadian rhythm leads to oscillations in resting core temperature that can vary by 0.5°C from early morning to mid-afternoon [18]. If the core temperature tolerated at exhaustion does not similarly show a circadian effect, and there is no evidence to suggest that it does, then the higher resting core temperatures in the afternoon should reduce tolerance time while wearing the protective clothing. This potential circadian influence has not been documented for the uncompensable heat stress conditions defined by wearing the NBC protective clothing and exercising in hot environments.

In certain military settings, personnel may be protected in cooler environments prior to donning their protective clothing and being exposed to hot environments. In other scenarios, however, exposure to hot environments for prolonged periods may be a requirement regardless of the clothing that is worn. Avenues for convective heat loss would be markedly reduced (or nonexistent) in these hot environments because of the high ambient temperatures. The potential differential impact of resting in a cool or hot environment prior to donning the NBC clothing and working in hot conditions has not been reported. In theory, any elevations in core temperature that occur prior to donning the protective ensemble should have a negative effect on tolerance time.

Melatonin is secreted by the pineal gland under the control of the suprachiasmatic nuclei with a circadian rhythm that follows our normal light and dark hours. Melatonin

blood levels begin to increase at about 2000 h reaching peak levels early in the morning at about 0300 h [19]. Thereafter, levels begin to decrease reaching baseline daylight values at about 0800 h [19, 20]. Although a cause and effect relationship has not yet been proven, the circadian rhythm for core temperature is inversely related to these changes in melatonin [19]. For example, as melatonin levels begin to increase, core temperature begins to fall, reaching its lowest value when melatonin levels peak. In addition, oral ingestion of melatonin can suppress the normal rise in core temperature that occurs during the morning and early afternoon daylight hours [20]. A fall in core temperature of 0.2 to 0.3°C during bed-rest studies has been reported following the ingestion of 1 to 10 mg of melatonin [19-26]. Because of the influence of the initial core temperature on tolerance time while wearing NBC clothing, it was with interest that we examined this potential hypothermic effect of melatonin ingestion. In theory, ingestion of melatonin in the early afternoon or during exposure to hot environments prior to donning the NBC clothing should extend tolerance time.

This report summarises the findings from 2 studies conducted using different doses of melatonin as part of work unit 6fe14 entitled, "Physiological Countermeasures Against Performance Degradation While Wearing NBC Ensembles in the Heat".

Methods

A detailed explanation of the methods followed for each study can be found in the articles by McLellan et al. [27, 28]. A brief description of the experimental design for each study is summarised below.

Study 1

Nine males performed four experimental sessions in random order separated by a minimum of 7 days and a maximum of 14 days. Most trials were performed on a weekly basis for a given subject. The following items were worn during each trial; underwear or jogging shorts, socks, lightweight cotton combat jacket and pants, semipermeable NBC overgarment, jogging shoes, impermeable overboots and gloves, and C4 respirator and cannister. The experimental sessions involved treadmill walking at 0.97 $m \cdot s^{-1}$ (3.5 $km \cdot h^{-1}$) for 45 min followed by 15 min of seated rest each hour in an environmental chamber set at 40°C, 30% relative humidity and a wind speed less than 0.1 $m \cdot s^{-1}$. The experimental trials consisted of 2 morning and 2 afternoon sessions with each trial involving the ingestion of 2 small capsules containing either placebo (lactose monohydrate) or melatonin (1 mg with lactose monohydrate filler) administered in a double-blind manner. The first capsule was ingested 2 hours prior to entry into the climatic chamber at 0730 h for the morning trials and 1130 h for the afternoon sessions. The second capsule was ingested just prior to beginning the heat-stress trial at either 0930 h or 1330 h for the morning and afternoon experiments, respectively. During the 2-hour period that intervened between the ingestion of the first and second capsule, subjects

were exposed to the same lighting conditions (approximately 500-700 lux) which involved either working at their desk in their office or watching a movie in a laboratory for the first hour, and then being instrumented and dressed during the second hour. Subjects were asked to avoid hard exhaustive exercise and the consumption of alcohol or nonsteroidal anti-inflammatory drugs for 24 h and caffeine for 12 h preceding each trial. Each session continued until either rectal temperature (T_{re}) reached 39.3°C, heart rate remained at or above 95% of peak heart rate for 3 min, nausea or dizziness precluded further exercise, the subject asked to be removed from the chamber, or the investigator removed the subject from the chamber. Subjects also performed a familiarisation trial which included all aspects of the experimental sessions, with the exception that no capsules were ingested, and used the same criteria for termination of the trial. This session was performed 7 days prior to the first experimental condition.

Study 2

As in study 1, nine males performed four experimental sessions in random order separated by a minimum of 7 days and a maximum of 14 days. The four trials began at the same time of day at approximately 0900 h and consisted of 2 hours of rest either at 23°C, 55% relative humidity or 40°C, 30% relative humidity with low background lighting while wearing underwear, jogging shorts, T-shirt, socks, lightweight cotton combat jacket and pants, and jogging shoes. For each of the trials, this rest period was followed by level treadmill walking at 0.97 $m \cdot s^{-1}$ (3.5 $km \cdot h^{-1}$) in the environmental chamber set at 40°C and 30% relative humidity with a wind speed less than 0.1 $m \cdot s^{-1}$. In addition to the other clothing, subjects wore a semipermeable NBC overgarment, impermeable overboots and gloves, and a C4 respirator with canister. During the rest period at 40°C, this additional clothing was warmed to the chamber temperature for 1 hour prior to being donned for the exercise. After thirty minutes of rest, subjects ingested one capsule containing 5 mg of melatonin with metamucil (filler) or a placebo capsule (metamucil) administered in a double-blind manner. Exercise at 40°C while wearing the NBC clothing continued until one of the end-point criteria outlined above for study 1 was reached. Subjects also performed a familiarisation trial 7 days prior to the first experimental condition.

Results

Study 1

Rectal Temperature

During the 2-hour period prior to heat-stress exposure, T_{re} was significantly elevated during the afternoon trials (Figure 1). The initial T_{re} recorded at the beginning of the heat-stress test was significantly higher during the afternoon (37.1°C) compared with the morning (36.8°C) trials and this difference between the morning and afternoon tests remained for the duration of the exposure (Figure 1). Melatonin had no impact on the T_{re} response during either the 2-hour period before the heat exposure or when the protective

clothing was worn in the chamber at 40°C. The T_{re} recorded at the end of the heat exposure was also significantly higher during the afternoon (39.2°C) compared with the morning (39.0°C) trials (Table 1). There was also no affect of melatonin ingestion or time of day on the rate of heat storage or the heat storage capacity (Table 1).

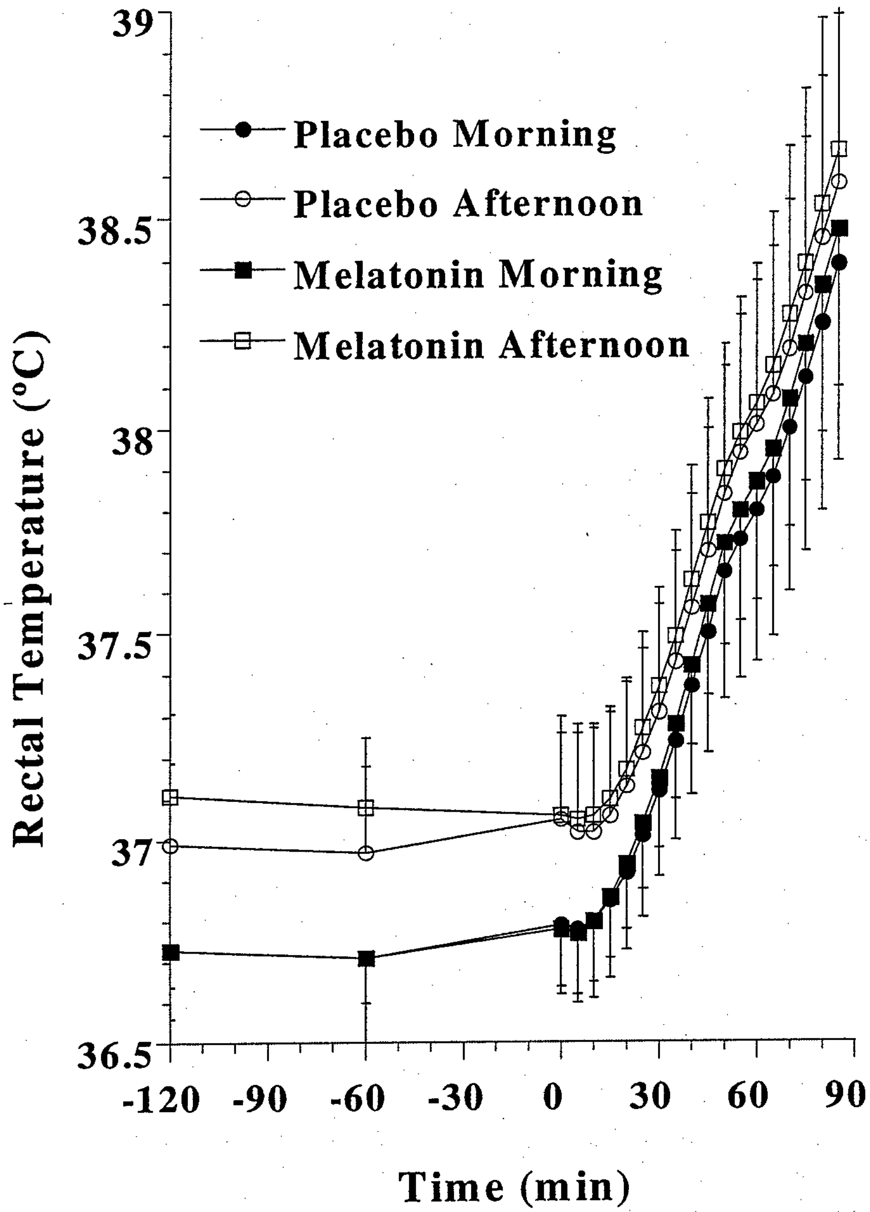

Figure 1 Changes in rectal temperature during the heat-stress trials conducted in the morning or afternoon at 40°C and 30% relative humidity while wearing NBC protective ensemble and ingesting either 1 mg melatonin or placebo capsules. Values are mean ± S.D. for n = 9. Rectal temperature was significantly increased throughout the afternoon trials and there was no effect of melatonin ingestion.

Table 1 Final rectal temperature, tolerance time, the rate of heat storage and the heat storage capacity for the heat-stress trials conducted in the morning or afternoon at 40°C and 30% relative humidity while wearing the nuclear, biological and chemical protective ensemble and ingesting either 1 mg melatonin or placebo capsules. Values are means (S.D.) for n = 9.

	Morning		Afternoon	
	Melatonin	**Placebo**	**Melatonin**	**Placebo**
*Final Rectal Temperature (°C)	39.04 (0.27)	38.97 (0.27)	39.22 (0.15)	39.08 (0.25)
Tolerance Time (min)	107.6 (19.6)	111.0 (22.0)	109.9 (23.3)	107.2 (19.0)
Rate of Heat Storage ($W \cdot m^{-2}$)	103.9 (23.7)	100.6 (24.0)	100.6 (21.8)	96.5 (21.2)
Heat Storage Capacity ($kJ \cdot kg^{-1}$)	16.1 (2.4)	16.1 (2.9)	16.0 (3.5)	15.1 (3.0)

* significant difference between the morning and afternoon trials.

Indices of Heat Tolerance

For the 36 trials, 16 were terminated when T_{re} reached 39.3°C. Exhaustion was stated as the reason for ending the exposure for 25% or 9 tests. For 7 of these 9 trials, T_{re} exceeded 38.8°C thus indicating that a substantial increase in body heat storage had occurred. For each of the 8 tests ended because of subject dizziness or nausea, T_{re} exceeded 38.8°C. For 2 of the 3 tests terminated because of the HR response exceeding 95% of the individual's peak value, T_{re} exceeded 38.8°C. Tolerance time was not affected by either the time of day or the ingestion of melatonin with values approaching 110 min for all trials (Table 1).

Study 2

Rectal Temperature

During rest at 23°C, a small but significant decline in T_{re} was recorded 90 min following the ingestion of the 5 mg dose of melatonin (Figure 2). This significant difference in T_{re} between the drug and placebo trials persisted as a main effect of temperature during the exercise period at 40°C while wearing the NBC clothing. The T_{re} recorded at the end of the exercise and heat-stress following the ingestion of melatonin during rest at 23°C was also significantly reduced (39.0°C) compared with the placebo (39.1°C) (Table 2). During the 2-hour rest period at 40°C, melatonin ingestion had no effect on the 0.5°C increase in T_{re}. Melatonin also did not affect the T_{re} response during the subsequent exercise while wearing the NBC clothing nor did the drug influence the T_{re} tolerated at exhaustion (Table 2). Differences in T_{re} during rest at 23°C or 40°C

became progressively more evident during the last 90 min and these differences remained during the exercise period.

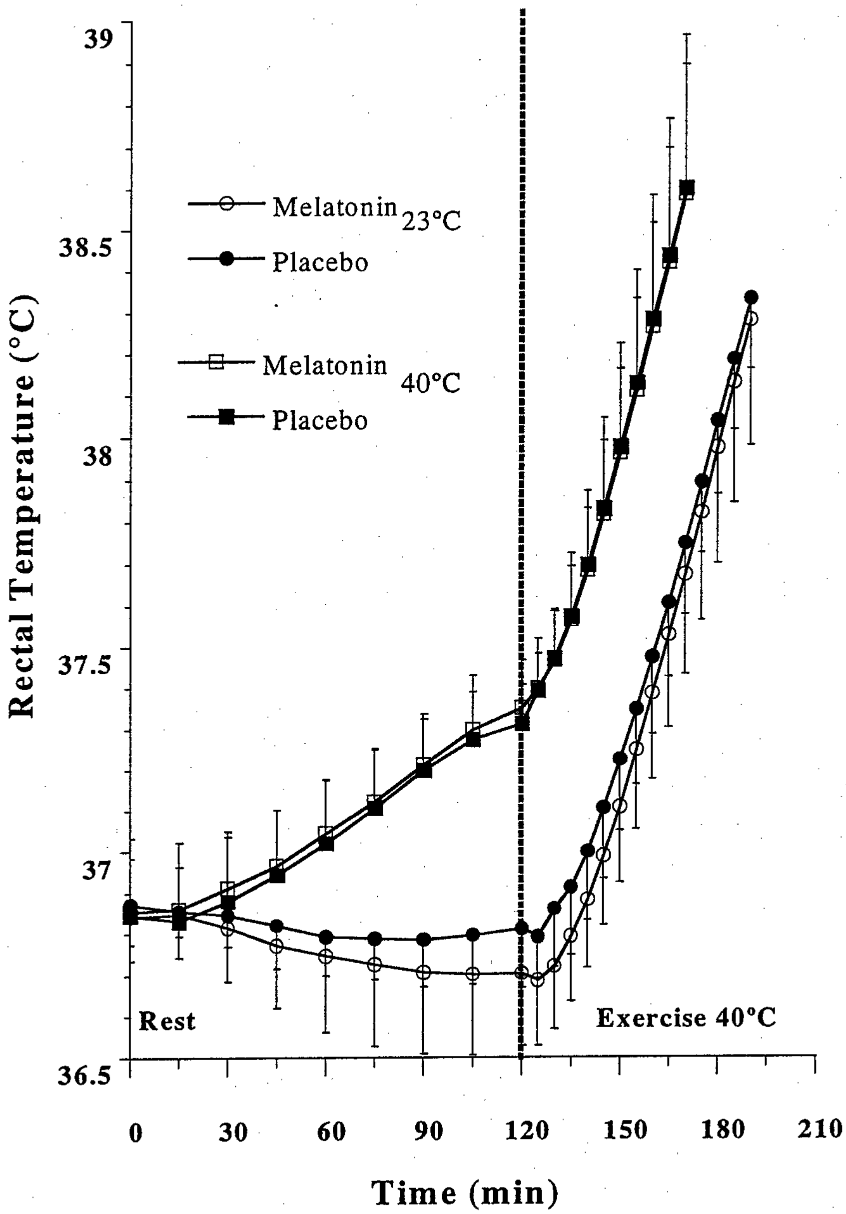

Figure 2 Changes in rectal temperature during the 2h rest period at either 23°C or 40°C while wearing combat clothing and during subsequent exercise at 40°C and 30% relative humidity while wearing the NBC protective ensemble. A 5mg dose of melatonin or a placebo capsule was ingested after 30 min of rest. Values are mean ± S.D. for n = 9. Rectal temperature decreased significantly following melatonin ingestion at 23°C compared with the placebo trial and remained lower during the exercise at 40°C. There was no effect of melatonin ingestion on the significant increase in rectal temperature that occurred during the rest and subsequent exercise period at 40°C.

Table 2 Final rectal temperature, tolerance time, the rate of heat storage and the amount of heat storage for the exercise period at 40°C and 30% relative humidity while wearing the nuclear, biological and chemical protective ensemble after the ingestion of 5 mg of melatonin or placebo during prior rest at either 23°C or 40°C. Values are means (S.D.) for n = 9.

	Prior Rest at 23°C		Prior Rest at 40°C	
	Melatonin	**Placebo**	**Melatonin**	**Placebo**
Final Rectal Temperature (°C)	38.96† (0.37)	39.07 (0.30)	38.99 (0.32)	39.05 (0.33)
*Tolerance Time (min)	92.8 (12.3)	95.3 (8.9)	63.4 (12.9)	64.4 (9.1)
Rate of Heat Storage ($W \cdot m^{-2}$)	121.9 (18.9)	120.9 (36.2)	109.7 (20.7)	112.6 (25.8)
*Heat Storage ($kJ \cdot kg^{-1}$)	17.5 (3.3)	17.6 (5.9)	10.9 (3.1)	12.0 (4.1)

* significant difference between prior rest at 23°C or 40°C. † significantly different from placebo.

Indices of Heat Tolerance

Tolerance time while wearing the NBC clothing was not affected by melatonin ingestion but was reduced by approximately 30 min following the 2h rest period at 40°C compared with prior rest in the cooler environment of 23°C (Table 2). For the 36 trials, exhaustion was stated as the reason for ending the exposure for 10 tests, dizziness for 8 trials, nausea and breathing difficulty for 1 each, and reaching a T_{re} of 39.3°C for 16 tests.

Discussion

Three main findings have evolved from these two studies. First, the ingestion of either two repeated 1 mg doses or one 5 mg dose of melatonin had little or no impact on heat tolerance or the thermoregulatory responses while wearing the NBC clothing. Second, trials conducted in the early afternoon were associated with an increased T_{re} tolerated at exhaustion that offset the circadian influence on resting rectal temperature, and thus, maintained tolerance times similar to trials conducted in the morning. Third, the rise in T_{re} that occurred during 2-hours of rest at 40°C subsequently reduced tolerance time in the NBC clothing by 30 minutes compared with trials involving prior rest at 23°C.

The hypothermic effect following the ingestion of 1 to 10 mg of melatonin has been well documented in humans [19-26] and thus the hypothermic response observed

during the resting phase at 23°C in study 2 is consistent with these previous reports. However, the 0.1°C fall in T_{re} during the second investigation was less than the 0.2-0.3°C decrease reported by these other authors. Most [19-22, 24-26] but not all [23], of these other studies involved controlled bed rest to eliminate the influence of activity, exposure to bright light and changing posture on core temperature. In the second study, posture was controlled in the seated position for 30 minutes before and 90 minutes following the ingestion of the melatonin. Tikuisis and Ducharme [29] have documented a 0.2°C fall in T_{re} during a 2-hour period in changing from the standing to the seated position and a further decrease of 0.3°C in changing to the supine position. In addition, Kräuchi et al. [30] have revealed that an orthostatic challenge in changing from the supine to the upright position negated the hypothermic effect of a 5 mg dose of melatonin. Thus, although posture was controlled in the present study, the orthostatic challenge that remained while in the seated position may have been sufficient to negate the greater hypothermic effect of melatonin that is observed during bed rest conditions [19-22, 24-26].

It was hypothesized that the two 1mg doses and the larger 5 mg dose of melatonin would decrease resting T_{re} at 23°C and that this decrease would increase tolerance time during exercise when the protective clothing was worn at 40°C. Although melatonin ingestion at rest was associated with a small but significant decrease in T_{re} that remained during the exercise and heat exposure while wearing the NBC clothing in study 2, there was also a small but significant reduction in the T_{re} tolerated at exhaustion during this melatonin trial. Thus, tolerance time remained similar to the placebo condition. Therefore, our hypothesis must be rejected. Given that there was little, if any, evidence to support an ergogenic effect following the melatonin ingestion and that the drug also has soporific side-effects [24, 25], we do not feel it is worthwhile to pursue additional studies during uncompensable heat stress that involve doses in excess of 5 mg.

Factors such as aerobic fitness [14] and heat acclimation [13, 15], which lower resting core temperature, are associated with increased tolerance time during uncompensable heat stress. Conversely, factors such as mild hypohydration [12, 14] or the post-ovulatory phase of the menstrual cycle [16, 17], which raise resting core temperature, reduce tolerance time. In addition, Gonzalez-Alonso [31] recently reported that well trained cyclists fatigued at the same core temperature of approximately 40°C during uncompensable heat stress regardless of changes to the initial core temperature or rates of heat storage. As a result, we hypothesized that the circadian influence on the initial resting T_{re} would decrease tolerance times during the uncompensable heat stress. The fact that T_{re} tolerated at exhaustion was increased during the afternoon trials was unexpected. Clearly, our hypothesis must be rejected at this time. Our subjects were highly motivated and did not appear to be ending their trials for any reasons other than discomfort or ethical constraints. In addition, when only those subjects were compared (n = 4) that ended all heat exposures below a T_{re} of 39.3°C, the significant difference in final T_{re} between the morning (38.8°C) and afternoon (39.1°C) trials persisted. Thus, it appears that the T_{re} tolerated at exhaustion is regulated at a higher temperature in the afternoon. This interpretation implies that it is not an absolute core temperature that the body can tolerate before exhaustion occurs, but rather a given increase in body heat content or delta core

temperature (see Table 1). This is an important finding since it means that work and rest schedules developed for the different NBC protective postures can be applied with equal confidence in the morning or afternoon.

In the second study, the 0.5°C increase in T_{re} following 2 hours of rest at 40°C was associated with a 30-minute decrease in tolerance time. Since subjects were walking at 3.5 $km \cdot h^{-1}$, this 30-min decrease in tolerance time would correspond to 1.75 km. Certainly the options for the commander are greatly decreased if core temperatures are elevated from prior rest or work in hot environments before donning the protective clothing. Thus, in contrast to the lack of effect on tolerance time with circadian variations in resting T_{re}, there are other situations where changes in resting T_{re} will have a significant influence on tolerance time and work performance. And it is important that military commanders understand the impact of these elevations in core temperature prior to donning the NBC protective ensemble. As shown in study 2, an increase in core temperature can result from simply resting in the hot environment while wearing normal work clothing. However, greater increases in core temperature would result if personnel were expected to exercise in these hot environments before there was a requirement to wear the NBC clothing. Together with the additional negative impact of beginning work sessions in a dehydrated state [32] due to inadequate fluid replacement opportunities, commanders should expect substantial differences in tolerance times when personnel are exposed to either cool or hot environments prior to donning the protective ensemble. Thus the use of the work and rest schedules developed for and authorised for use by the Directorate of Nuclear, Biological and Chemical Defence are appropriate only for personnel who are well rested and protected in a cool environment prior to donning the NBC ensemble and being exposed to hot conditions.

In summary the following conclusions were generated from these two studies with varying doses of melatonin. First, 1 to 5 mg doses of melatonin had no impact on tolerance to the heat stress of wearing NBC protective clothing and exercising in hot environments. Second, trials conducted in the early afternoon were associated with an increased rectal temperature tolerated at exhaustion that offset the circadian influence on resting rectal temperature, and thus, maintained tolerance times similar to trials conducted in the morning. Third, elevations in core temperature that occur during rest in a hot environment significantly impaired tolerance while wearing protective clothing and exercising in the heat. The use of work and rest schedules for NBC operations can be used throughout the day but only when subjects are rested and not exposed to hot environments prior to donning the NBC clothing.

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This report summarises the findings from 2 studies which examined whether the reported hypothermic effect of melatonin ingestion increased tolerance to the heat stress of wearing NBC protective clothing. In the first study, trials were conducted either in the morning or afternoon, 2 each in the morning (0930 h) and afternoon (1330 h) following the double-blind ingestion of either two placebo or two 1 mg capsules of melatonin. The heat stress test consisted of intermittent walking and seated rest at 40°C and 30% relative humidity while wearing NBC protective clothing. In the second study, subjects performed 4 trials which involved 2h of rest in combat clothing at either 23°C or 40°C followed by exercise at 40°C while wearing the NBC ensemble. A single 5 mg dose of melatonin was ingested following 30-min of rest. In the first study, rectal temperature (T_{re}) was not affected by melatonin ingestion but T_{re} was increased during the afternoon trials by 0.3°C compared with the morning exposures and these differences remained throughout the heat stress such that final T_{re} was also increased for the afternoon (39.2°C) versus the morning (39.0°C) trials. Since the rate of heat storage was similar, tolerance times (108, 111, 110 , and 107 min for the morning melatonin and placebo trials, and the afternoon melatonin and placebo trials, respectively) were not different among the trials. During the second study, T_{re} during rest at 23°C decreased significantly from 36.8°C to 36.7°C following the ingestion of the drug, whereas values during the placebo trial did not change. The lower T_{re} response during the melatonin trial at rest remained during the exercise in the heat while wearing the NBC protective clothing. However, since the T_{re} tolerated at exhaustion also was significantly lower for the melatonin (39.0°C) compared with the placebo (39.1°C) trial, tolerance times approximated 95 min in both conditions. During rest at 40°C, melatonin did not affect the T_{re} response which increased significantly over the rest period from 36.9°C to 37.3 °C. This increase in T_{re} during the rest period prior to donning the protective clothing decreased tolerance time approximately 30 min compared with the trials that involved prior rest at 23°C. Three conclusions evolved from these studies. First, 1 to 5 mg doses of melatonin had no impact on tolerance to the heat stress of wearing NBC protective clothing and exercising in hot environments. Second, trials conducted in the early afternoon were associated with an increased rectal temperature tolerated at exhaustion that offset the circadian influence on resting rectal temperature, and thus, maintained tolerance times similar to trials conducted in the morning. Third, elevations in core temperature that occur during rest in a hot environment significantly impaired tolerance while wearing protective clothing and exercising in the heat. The use of work and rest schedules for NBC operations can be used throughout the day but only when subjects are rested and not exposed to hot environments or conditions that elevate core temperatures prior to donning the NBC clothing

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